



**Karolinska
Institutet**

**Department of Medical Epidemiology and Biostatistics
(Karolinska Institutet) & Department of Epidemiology and Public
Health (National University of Singapore)**

HEALTH OUTCOMES ASSOCIATED WITH COGNITIVE IMPAIRMENT

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i sal Petré, Nobels väg 12B,
Karolinska Institutet, Solna

Fredagen den 7:e oktober, 2011, kl 09.00

av

Kaavya Narasimhalu

BA

Huvudhandledare:

Professor Chia Kee Seng
National University of Singapore
Dept. of Epidemiology and Public Health

Bihandledare:

Professor Nancy Pedersen
Karolinska Institutet
Dept. of Medical Epidemiology & Biostatistics

Ass. Professor Anna Bennet
Karolinska Institutet
Dept. of Medical Epidemiology & Biostatistics

Ass. Professor Christopher Chen
National University of Singapore
Dept. of Pharmacology

Fakultetsopponent:

Professor Kenneth Rockwood
Dalhousie University
Division of Geriatric Medicine
Division of Neurology

Betygsnämnd:

Professor Åke Wahlin
Stockholm University
Dept. of Psychology

Professor Niklas Hammar
Karolinska Institutet
Institute for Environmental Medicine

Ass. Professor Miia Kivipelto
Karolinska Institutet
Aging Research Center

Stockholm 2011

ABSTRACT

In this thesis, we aimed to determine whether persons with cognitive impairment no dementia (CIND) were at higher risk for negative health outcomes, and if so, to stratify persons with CIND into high and low risk groups. We also aimed to determine the whether persons with CIND had a higher risk of negative health outcomes based on their underlying familial risk, or whether difficulties with medication played a part in the development of negative health outcomes. Lastly, we aimed to determine whether cardiovascular and antidepressant medication use modified the relationship between CIND and dementia.

In Studies I and II, non-demented stroke patients who were recruited as part of the ESPRIT trial were followed up for up to five years. In Study I, a novel method of stratifying CIND based on the severity of impairment, was compared to established MCI subtypes in the ability to predict dementia. Having CIND-moderate increased the risk of dementia more than six times (HR 6.43, CI 1.30-31.7) while having multiple domain mild cognitive impairment with amnesic components increased the risk of dementia more than five times (HR 5.77, CI 1.19-28.0).

In Study II, the effect of CIND and CIND severity on dependency, vascular events, and death were analyzed. Patients with CIND were three times more likely to become dependent (HR 3.77 CI 1.52 -9.37) and three times more prone to mortality (HR 3.27 CI 1.06-10.1). CIND severity was able to discriminate those at high risk of death, with patients with CIND-moderate (HR 3.81 CI 1.14-12.8) almost four times more likely to die as compared to non-cognitively impaired patients.

In Studies III and IV, non-demented community dwelling twins who were assessed cognitively as part of a dementia study, HARMONY, were followed up negative outcomes with population-based registers. In Study III, we investigated the effect of CIND and Subjective Cognitive Impairment (SCI) on negative outcomes. CIND predicted hospitalization for dementia, death, and hospitalization in GEE analyses but not in within-pair analyses. SCI predicted dementia in both GEE and with pair analyses but only predicted hospitalization in GEE analyses. These results suggested that the relationship between CIND and negative health outcomes is confounded by genetic and shared environmental influences while SCI is independently associated with negative health outcomes. Additionally, we found that difficulty with medication was an independent risk factor for both dementia and death.

In Study IV, we aimed to determine whether medication use was associated with dementia, and whether individuals with CIND, SCI, or depression received more medication than their unimpaired counterparts. Antidepressant use, particularly the use of Selective Serotonin Reuptake Inhibitors (SSRIs) doubled the risk of dementia regardless of depression or cognitive status. Cardiovascular medications, particularly antihypertensive and lipid lowering agents halved the risk of dementia. In addition, we find that persons with CIND and SCI received less cardiovascular and more antidepressant medications than their non-impaired counterparts.

Overall, this thesis shows that persons with CIND are at increased risk of negative health outcomes such as dementia, death, hospitalization, and disability. CIND appears to be associated with negative health outcomes both due to difficulties with medication and due to the fact that CIND acts as a marker of underlying disease processes. In addition, we find that persons with CIND get less cardiovascular medications and more antidepressant medications, both of which increase the risk of dementia. These findings suggest that persons with CIND are a high-risk group in which greater vigilance by health professionals may bring benefits.